



## Bronchial Hyperresponsiveness in the Assessment of Asthma Control

### Airway Hyperresponsiveness in Asthma: Its Measurement and Clinical Significance

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The two key pathophysiologic features of asthma are bronchial hyperresponsiveness (BHR) and airway inflammation. Symptoms and lung function are the most accessible clinical markers for the diagnosis of asthma as well as for assessing asthma control using the most effective treatment of asthma, inhaled corticosteroids (ICS). However, BHR and inflammation usually take longer to resolve using ICS compared with symptoms and lung function. BHR can be assessed using “direct” stimuli that act on the airway smooth muscle (eg, methacholine) or “indirect” stimuli that require the presence of airway inflammation (eg, exercise, osmotic stimuli). Although there are practical limitations in using BHR to assess asthma control, efforts have been made to make BHR more accessible and standardized. Some studies have demonstrated that treatment aimed to decrease BHR with direct stimuli can lead to improved asthma control; however, it often results in the use of higher doses of ICS. Furthermore, BHR to direct stimuli does not usually resolve using ICS because of a fixed component. By contrast, BHR with an indirect stimulus indicates a responsive smooth muscle that occurs only in the presence of inflammation sensitive to ICS (eg, mast cells, eosinophils). BHR to indirect stimuli does resolve using ICS. Because ICS target both key pathophysiologic features of asthma, assessing indirect BHR in the presence of ICS will identify resolution or persistence of BHR and airway inflammation. This may provide a more clinically relevant marker for asthma control that may also lead to improving the clinical usefulness of ICS.

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**Abbreviations:** BHR = bronchial hyperresponsiveness; EIB = exercise-induced bronchoconstriction; FENO = fraction of exhaled nitric oxide; ICS = inhaled corticosteroids; PC<sub>20</sub> = provocative concentration causing a 20% fall in FEV<sub>1</sub>

The current Global Initiative for Asthma guidelines define asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.<sup>1</sup> The chronic inflammation is associated with bronchial hyperresponsiveness (BHR), which is

responsible for recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. Inhaled corticosteroids (ICS), which act via a wide variety of mechanisms to reduce airway inflammation and BHR, are the most effective treatment of asthma.<sup>2</sup> Symptoms and lung function are the most accessible markers of asthma and help clinicians to identify asthma and assess its response to treatment. Unfortunately, these markers have limitations in that they often relate poorly to airway inflammation or BHR.<sup>3,4</sup> A major limitation is the absence of a dose-response curve to ICS for both symptoms and lung function. That is, in many people with asthma, the same improvements in symptoms and lung function are observed after a short period using either low or high doses of ICS.<sup>5</sup> A requirement of the guidelines is that a clinician must monitor the clinical signs of asthma

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and minimize the dose of ICS accordingly to avoid unwanted side effects of ICS. The flat dose-response curve for improvement in symptoms and lung function makes it difficult to use these markers to identify the minimal effective dose of ICS and to identify the optimal dose to resolve inflammation and BHR.

### ASTHMA CONTROL

Asthma control has been defined as the extent to which the manifestations of asthma have been removed by treatment.<sup>6</sup> This definition considers the effects of ICS on symptoms and lung function when defining control. It is recommended that the assessment of asthma control incorporate the dual components of current clinical control (eg, symptoms, use of  $\beta_2$ -agonist, and lung function) as well as future risk (eg, exacerbations and decline in lung function). However, following ICS use the resolution of symptoms and lung function may not identify resolution of airway inflammation or BHR.<sup>3,5,7</sup>

There is a recognized need to assess responses to ICS using an accessible and reliable marker of asthma pathophysiology. Evidence for this is found in the persistent levels of poor asthma control, even in the presence of known effective therapies and updated guidelines for their use.<sup>8</sup> There are currently no therapies that possess the broad antiinflammatory effects of ICS. Thus, an alternative approach to improve asthma control may be via the use of objective markers that assess the key pathophysiologic features of asthma, BHR, and/or inflammation.

In 2006, Bukstein and colleagues<sup>9</sup> suggested that the ideal objective measure for the purposes of assessing ICS in asthma should be simple, practical, meaningful, discriminatory, responsive to change, and reflective of short- and long-term control, while being applicable to patients, clinicians, and researchers. Over the past 10 years, there have been many attempts to explore the use of either BHR or markers of inflammation (eg, sputum eosinophils, fraction of exhaled nitric oxide [FENO]) to identify the effect of ICS.<sup>10-13</sup> The goal is to find a tool that provides evidence for reduction of airway inflammation and BHR, which both take longer to resolve with ICS when compared with symptoms and lung function. A tool that can assess a successful resolution of these features would improve the clinical efficacy of ICS and may provide better evidence for asthma control.

### BHR AS A MARKER OF ASTHMA CONTROL

There are two categories of tests for BHR, both defined by the mechanism by which they cause airway narrowing. Direct stimuli are the pharmacologic agents,

such as histamine and methacholine, that act directly on specific receptors on the bronchial smooth muscle causing it to contract.<sup>14</sup> Persons with asthma are usually hyperresponsive to these agents. BHR to the direct stimuli in people with asthma is associated with airway inflammation (eg, eosinophils and mast cells) that is sensitive to treatment with ICS.<sup>15,16</sup> However, the mechanism by which the airways narrow to these direct stimuli does not depend on the presence of airway inflammation. Further, a relationship between airway sensitivity to a direct stimulus and severity of airway inflammation is inconsistent.<sup>4,17</sup> This can be explained by other factors, such as baseline airway caliber and the degree of airway remodeling, that may or may not be affected by treatment with ICS.<sup>14</sup>

There are also stimuli that act indirectly to cause the airways to narrow. These indirect stimuli act by the release of contractile mediators from inflammatory cells within the airway that include histamine, prostaglandins, and leukotrienes.<sup>18</sup> These indirect stimuli commonly include exercise, eucapnic hyperpnea with dry air, hyperosmolar aerosols (eg, saline or mannitol), and the pharmacologic agent adenosine monophosphate. Tests that act indirectly are clinically the most relevant because most attacks of asthma in daily life are caused by stimuli that act indirectly. A positive response to a test that uses an indirect stimulus is consistent with the presence of inflammatory cells and smooth muscle responsive to the concentration of mediators they release. This conclusion is supported by studies that have compared both direct and indirect tests for BHR and the relationship to sputum eosinophils in the same subjects with asthma.<sup>15,19</sup>

The use of BHR to assess ICS is, from a practical viewpoint, currently difficult to implement, as testing equipment is usually only available in hospital laboratories or specialist centers. More recently, a test for BHR using a dry powder of mannitol has become available as a test kit, making it easier to challenge using a standardized operating procedure at the point of need.<sup>20</sup> Tests for BHR have an important use in confirming the presence of asthma in persons with normal lung function to identify the requirement of ICS. If BHR is reduced or resolved following treatment with ICS it is considered that airway inflammation is also reduced or resolved.

### DIRECT BHR AND ASTHMA CONTROL

Although BHR to agents that act directly usually decreases during treatment with ICS, it does not resolve. Decreases in BHR to direct agents have been shown in response to both low and high daily doses of ICS over both short-term (weeks) and long-term (months, years), and this occurs in association with the well-recognized clinical improvements associated

with regular ICS (Fig 1).<sup>10,21-25</sup> However, the persistence of BHR of the airway smooth muscle to either methacholine or histamine is unlikely simply to be reflecting changes in airway inflammation. Thus, there are two components of BHR to direct stimuli: a variable component reflecting airway inflammation or disease activity and a fixed component reflecting airway remodeling.<sup>26</sup>

A comparison was made using a treatment strategy aimed at reducing airway hyperresponsiveness to a direct stimulus (BHR strategy) to a parallel group who were treated based on recommendations in the existing guidelines (reference strategy) to investigate if BHR was a useful clinical tool for assessing efficacy of ICS.<sup>10</sup> Sont and colleagues<sup>10</sup> reported that in adults with asthma studied over a 2-year period using the BHR strategy there was a 1.8-fold lower incidence of mild exacerbations and a significantly sustained improvement in prebronchodilator FEV<sub>1</sub>. This improved asthma control was also associated with improvements in the reticular layer thickness beneath the epithelium, suggesting that improvements in airway remodeling were made in the BHR strategy group. This improvement, however, was achieved with double the dose of ICS in the BHR group (~800 µg) compared with the reference strategy group (~400 µg). Furthermore, the BHR, measured as the provoking concentration causing a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) to methacholine of 0.47 mg/mL before treatment, was only marginally reduced using the BHR strategy (increase in PC<sub>20</sub> of 1.1 doubling dose). This confirmed previous studies showing that long-term treatment with ICS does not necessarily reduce BHR to methacholine to anywhere near the normal range (> 16 mg/mL) (Fig 1).

Other studies, however, have not confirmed the clinical benefits of assessing ICS using a BHR strategy

of assessment using methacholine in children. Nuijsink and colleagues<sup>11</sup> used a similar study design in children over a 2-year period but found no increase in the number of symptom-free days using the BHR strategy. They did, however, observe a better prebronchodilator FEV<sub>1</sub> in a subgroup of children with allergic asthma.<sup>11</sup> As with the study by Sont et al,<sup>10</sup> this also was achieved with a higher dose of ICS in the BHR strategy. Although a decrease in BHR was observed for both the reference and BHR strategies, BHR persisted following treatment. Finally, a study over a shorter duration (40 weeks) in adults found no advantage in using a BHR strategy with methacholine in terms of improvements in symptoms, peak expiratory flow, or β<sub>2</sub>-agonist use.<sup>27</sup> Again, the BHR strategy led to the use of higher doses of ICS either with or without the addition of a long-acting β<sub>2</sub>-agonist. Once again, BHR to methacholine persisted and did not differ between the BHR and reference strategy groups.

#### INDIRECT BHR AND ASTHMA CONTROL

BHR to indirect stimuli decreases following treatment with ICS. The distinct difference between direct and indirect stimuli is that BHR to indirect stimuli can resolve over a period that a patient can be expected to comply with treatment with ICS. Resolution of exercise-induced bronchoconstriction (EIB) is a clinically relevant example of this outcome using treatment with ICS.<sup>28,29</sup> Many studies have demonstrated that the degree of BHR to indirect stimuli is related to the presence of eosinophils and mast cells,<sup>15,30,31</sup> both of which are known to decrease in number following treatment with ICS.<sup>32</sup> For example BHR to hypertonic saline was strongly associated with higher levels of eosinophils (odds ratio, 4.36, 1.70-11.20) and mast cells (odds ratio, 7.46, 2.48-22.75).<sup>30</sup> As the mediators from these inflammatory cells are those that cause the response to indirect stimuli, resolution of indirect BHR following treatment with ICS is a clinically meaningful outcome to identify control of inflammation.<sup>33</sup>

The efficacy of ICS in attenuating EIB is well described.<sup>34</sup> Importantly, there is a dose-response effect on the reduction in the percent fall in FEV<sub>1</sub> following exercise. Pedersen and Hansen<sup>5</sup> demonstrated, in children with asthma, that 4 weeks of budesonide was significantly more effective for inhibiting EIB at a dose of 400 µg compared with a dose of 200 µg, and 200 µg was more significantly effective than 100 µg (Fig 2A). In contrast, the dose effect on symptoms and lung function (peak expiratory flow) plateaued and remained unchanged after 100 µg (Fig 2B). As the children still had EIB on the lower doses of ICS, the reductions in symptoms and lung function were not reflective of the clinically relevant issue

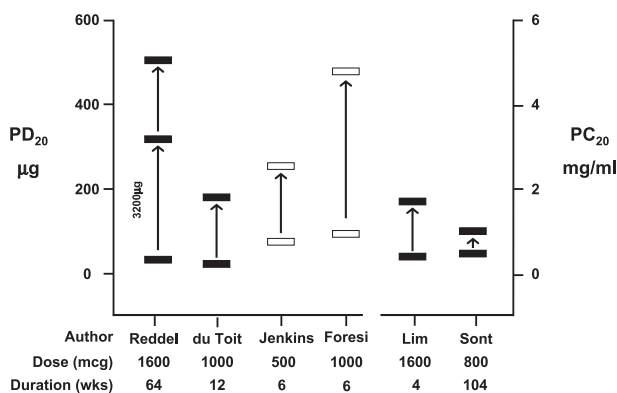


FIGURE 1. A summary of the improvement in bronchial hyperresponsiveness (BHR) following treatment with inhaled corticosteroids (ICS) (□: fluticasone; ■: budesonide or beclomethasone; expressed as PD<sub>20</sub> or PC<sub>20</sub>) from six studies using either histamine<sup>21</sup> or methacholine.<sup>10,22-25</sup> BHR to direct stimuli remains in the presence of high doses of ICS over short- and long-term treatment periods. PC<sub>20</sub> = provoking concentration causing a 20% fall in FEV<sub>1</sub>; PD<sub>20</sub> = provoking dose causing a 20% fall in FEV<sub>1</sub>.

(ie, EIB). A recent study measuring sputum eosinophils has provided some further insight into these findings. Duong and colleagues<sup>31</sup> performed a similar study assessing the impact of doubling doses of ICS over 3 weeks in adults with asthma. They found that higher levels of eosinophils were associated with more significant percent falls in FEV<sub>1</sub> following exercise. In response to low doses of ICS, those with higher levels of sputum eosinophils (>5%) had only a modest reduction in EIB that plateaued (Fig 3). However, when the same subjects received a higher dose of ICS, a more rapid attenuation in EIB was achieved. For those with lower levels of eosinophils (<5%) who also had milder EIB, rapid reduction in EIB was

observed in 3 weeks on either high- or low-dose ICS; however, this was not long enough to abolish EIB. The persistence of EIB may have been due to the persistence of mast cells, which play an important role in EIB and are known to decrease in number less rapidly than eosinophils.<sup>35</sup> This demonstrates the usefulness of severity of EIB to identify the minimum dose of ICS and suggests that ongoing assessment of EIB to resolution during ICS treatment is useful.

Exercise is a difficult test to perform, for practical reasons, and other indirect tests are easier to administer and provide similar usefulness for identifying responses to ICS.<sup>20</sup> For example challenges using a dose-response protocol, such as aerosols of mannitol

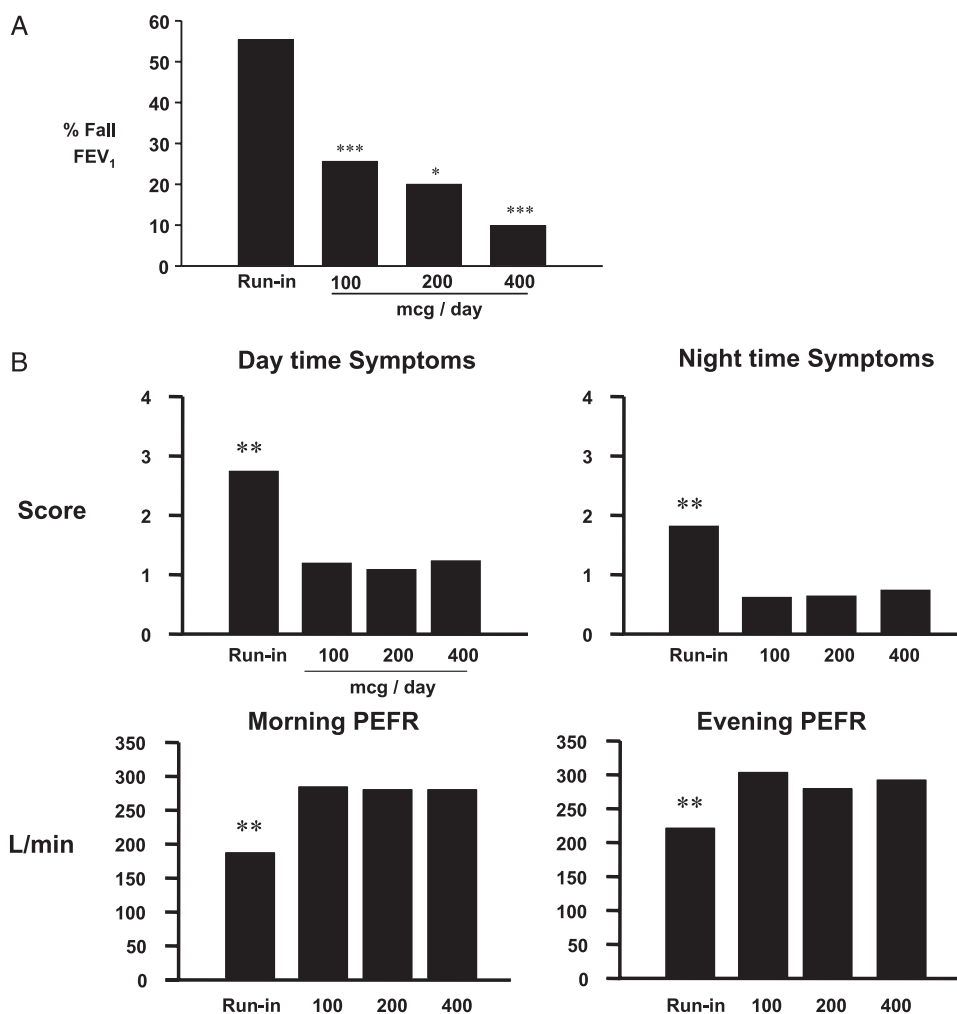


FIGURE 2. (A) Mean values for the fall in FEV<sub>1</sub> expressed as a percentage of the baseline value for FEV<sub>1</sub> after exercise in 19 children with asthma who received different doses of budesonide in random order for 4 weeks. The data demonstrate a dose-response relationship between severity of exercise-induced asthma and the dose of inhaled steroid; 100 µg was more effective than placebo (\*\**P* < .0001), 200 µg was more effective than 100 µg (\**P* < .01), and 400 µg was more effective than 200 µg (\*\**P* < .0001). (B) The change in symptoms and PEFR in relation to dose of inhaled budesonide in children with asthma who performed the exercise challenge as shown in A. The data illustrate that symptoms and PEFR resolved at low doses of budesonide, whereas resolution of EIB required higher doses. EIB = exercise-induced bronchoconstriction; PEFR = peak expiratory flow rate. \*\**P* < .001 compared with active treatments. (Adapted from data from Pedersen and Hansen.<sup>5</sup>)

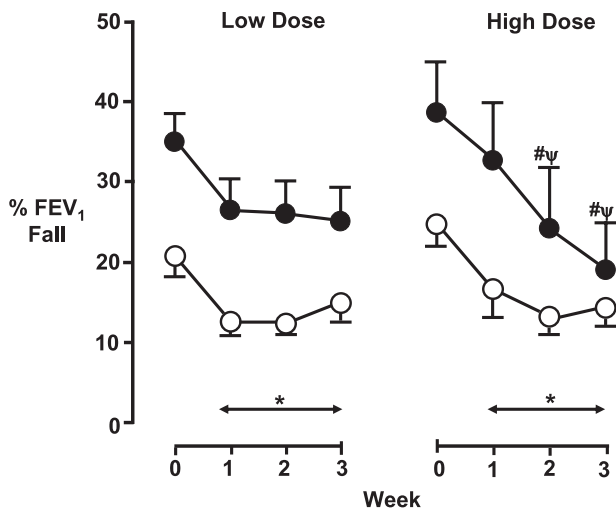


FIGURE 3. Percentage fall in FEV<sub>1</sub> after exercise in response to low-dose (40 or 80 μg) and high-dose (160 or 320 μg) ciclesonide according to baseline sputum eosinophil counts. A group with high eosinophils (>5%, n = 10) (●) demonstrated a significantly greater reduction in EIB from baseline using high-dose ICS compared with a low-dose ICS over 3 weeks. A group with low levels of eosinophils (<5%, n = 13) (○) showed low- and high-dose ICS has similar benefits on EIB. Changes from baseline were compared within a group (\*) and between groups (#) for each dose level at *P* < .05. Only the sputum eosinophilic group showed a significantly greater change from baseline to high ICS dose compared to low ICS dose (ψ) (*P* < .05). See Figure 2 for the expansion of the abbreviation. (Reprinted with permission from Duong et al.<sup>31</sup>)

or 4.5% saline, can be used to identify the potential for EIB in persons with asthma. The provoking dose of mannitol causing a 15% fall in FEV<sub>1</sub> predicted the severity of EIB in steroid-naïve patients with asthma.<sup>36,37</sup> Airway responses to hyperosmolar aerosols are markedly inhibited or even abolished following treatment with ICS.<sup>21,33,38,39</sup> In the studies of Brannan et al<sup>39</sup> and Koskela et al,<sup>33</sup> the resolution of BHR to mannitol was observed in association with the expected attenuation of symptoms and lung function to ICS over the period of treatment. Conversely, the airway sensitivity to mannitol returns or increases following withdrawal of ICS in patients with asthma who are clinically stable.<sup>40</sup> Increases in the airway reactivity to mannitol as well as increases in eosinophils were predictive of an exacerbation during down-titration of ICS dose.<sup>40</sup>

Using an indirect stimulus to assess BHR during ICS treatment, as shown above in subjects with known asthma, provides useful information on whether there is a need to adjust ICS dosage. This approach is likely to result in optimal asthma control using a minimum dose of ICS as required by the Global Initiative for Asthma guidelines. Using an indirect stimulus to assess BHR during ICS treatment in those presenting with an unclear diagnosis who are currently taking ICS is also useful. If a positive response to an indirect stimulus is documented it is confirmation of currently active asthma. If the response is negative, the asthma is not active at the time and may have been mild initially, or

the patient may have even been misdiagnosed on the basis of symptoms. In contrast, if the same subject on ICS had BHR to a direct stimulus, it would not be possible to confirm whether the asthma is currently active or if BHR is “fixed” because of airway remodeling. This can be important considering the recommendations to withdraw long-acting β<sub>2</sub>-agonists in those taking combination therapy.<sup>41</sup> Normal lung function with no BHR to an indirect stimulus would provide evidence that a regular long-acting β<sub>2</sub>-agonist is probably not warranted. It would be more difficult to come to the same decision if BHR to a direct stimulus was present.

BHR using indirect stimuli to monitor ICS has advantages over both sputum eosinophils and FENO. Monitoring ICS using sputum eosinophils is only possible in subjects who have the eosinophilic inflammatory phenotype. However, there is evidence that noneosinophilic phenotypes will also benefit from treatment with ICS.<sup>42</sup> BHR to indirect tests can also be present in subjects with the neutrophilic and paucigranulocytic inflammatory phenotypes.<sup>43,44</sup> This suggests that mast cells are still playing an active role in all these phenotypes with indirect BHR and that continued treatment with ICS would be beneficial and could also be monitored using indirect stimuli. Both the eosinophils and FENO are rapidly responsive to the effects of ICS.<sup>45</sup> Unlike eosinophils,<sup>12</sup> the role of FENO in monitoring ICS is still unclear even after a number of large clinical trials.<sup>13</sup> There is evidence for subjects with normal FENO levels being hyperresponsive to mannitol,<sup>15,44</sup> again emphasizing the role of the mast cell and the inability of FENO to identify its presence and activity.

EIB is common in persons with active asthma and the presence or resolution of EIB has been used as a clinically relevant outcome to monitor dose and response to ICS.<sup>5,28,46</sup> Hard evidence is currently lacking to indicate if asthma can be managed better and more economically using indirect stimuli other than exercise; however, there is a significant body of evidence to suggest that further investigations are warranted.

## CONCLUSION

When treating asthma using ICS, symptoms and lung function are not adequate markers of asthma control when compared with measurements of asthma pathophysiology. Although treatment guided by BHR with direct stimuli can be an effective marker of asthma control in some studies, it usually results in the use of high doses of ICS. High doses of ICS carry increased risk for unwanted side effects and paradoxically the BHR to direct stimulus still remains. The advantage of measuring BHR using indirect stimuli to monitor ICS is that the end point of treatment is resolution of

BHR to the indirect stimulus. Further BHR to an indirect stimulus indicates a responsive smooth muscle in the presence of inflammation. Measuring a reduction in BHR using an indirect stimulus in the presence of ICS indicates reduction in airway inflammation. Thus, BHR using stimuli that act indirectly may provide a marker of asthma control that is superior to asthma control defined by symptoms and lung function.

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